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☐ 1: Electrophoresis 1997 Mar-Apr;18(3-4):582-7

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Analysis of polypeptide expression in benign and malignant human breast lesions.

Franzen B, Linder S, Alaiya AA, Eriksson E, Fujioka K, Bergman AC, Jornvall H, Auer G.

Unit of Cell and Molecular Analysis, Karolinska Institute and Hospital, Stockholm, Sweden.

Results of two-dimensional electrophoresis (2-DE) analyses of human breast carcinoma are described. Tumor cells were extracted and purified from breast carcinomas with different proliferative indeces and degrees of genomic stability. Cells purified from fibroadenoma tissue served as controls for benign cells. The following results were observed: (i) Analysis of samples from different areas of the same tumor showed a high degree of similarity in the pattern of polypeptide expression. Similarly, analysis of two tumors and their metastases revealed similar 2-DE profiles. (ii) In contrast, large variations were observed between different lesions with comparable histological characteristics. Larger differences in polypeptide expression were observed between potentially highly malignant carcinomas compared to comparisons of less malignant lesions. These differences were in the same order of magnitude as those observed comparing a breast carcinoma to a lung carcinoma. (iii) The levels of all cytokeratin forms resolved (CK7, CK8, CK15, and CK18) were significantly lower in carcinomas compared to fibroadenomas. (iv) The levels of high molecular weight tropomyosins (1-3) were lower in carcinomas compared to fibroadenomas. The expression of tropomyosin-1 was found to be 1.7-fold higher in primary tumors with metastatic spread to axillar lymph nodes compared to primary tumors with no evidence of metastasis ($p < 0.05$). (v) The expression of proliferating cell nuclear antigen (PCNA) and some members of the stress protein family (pHSP60, HSP90, and calreticulin) were higher in carcinomas. We conclude that malignant progression of breast carcinomas results in large heterogeneity in polypeptide expression between different tumors, but that some common themes such as decreased expression of cytokeratin and tropomyosin polypeptides can be discerned.

PMID: 9150945 [PubMed - indexed for MEDLINE]

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Expression and roles of heat shock proteins in human breast cancer.

Yano M, Naito Z, Tanaka S, Asano G.

Department of Pathology, Nippon Medical School, Bunkyo-ku, Tokyo.

Heat shock proteins (hsps) are thought to play important roles in the cell cycle and various processes of carcinogenesis. Therefore, we evaluated the expression of hsps, mainly hsp90 and hsp70, in human breast cancer tissues. Hsp90alpha mRNA was expressed at much higher levels in the cancerous tissue than in the non-cancerous tissue. In addition, a close correlation between hsp90alpha mRNA expression and the proliferating-cell-nuclear-antigen labeling index (PCNA LI) was observed for the cancerous tissue. These findings suggest that increased expression of the hsp90alpha isoform may play a role in cell proliferation. On the other hand, hsp90beta mRNA expression was significantly higher in poorly differentiated carcinomas than in well differentiated carcinomas of the breast. The intracellular localization of hsp70 was consistent with that of ubiquitin. In specimens showing hsp70 in the nucleus, the PCNA LI was significantly high. Hsc73 mRNA, a member of the hsp70 family, was also expressed at higher levels in cancerous tissues associated with a high PCNA LI than in non-cancerous tissues. These results suggest that hsp90alpha may play a role in cancer cell proliferation and that hsp90beta may contribute to cell differentiation and structural constitution. In addition, hsp70, especially hsc73, is related to ubiquitin and seems to be a marker for cancer proliferation.

PMID: 8878452 [PubMed - indexed for MEDLINE]

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☐ 1: Leukemia 1996 Jun;10(6):994-9

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Mechanisms of glucocorticoid resistance in human leukemic cells: implication of abnormal 90 and 70 kDa heat shock proteins.

Kojika S, Sugita K, Inukai T, Saito M, Iijima K, Tezuka T, Goi K, Shiraishi K, Mori T, Okazaki T, Kagami K, Ohyama K, Nakazawa S.

Department of Pediatrics, Yamanashi Medical University, Japan.

The unliganded glucocorticoid receptor is a multi-oligomer complex consisting of a ligand-binding protein with which two 90 kDa heat shock proteins (hsp90s) are associated. Upon binding of glucocorticoid to the receptor, the ligand-binding protein, which dissociated from hsp90s, enters the nucleus, binds to a specific site in DNA, and thus transmits signal(s). The 70 kDa heat shock protein (hsp70) also works as a molecular chaperone when the ligand-binding protein enters the nucleus. Regarding the mechanisms of glucocorticoid resistance, a decreased expression of glucocorticoid receptor and a mutant protein with low ligand binding affinity have been reported. In the present study, to address other mechanisms of glucocorticoid resistance, we examined the expression of hsp90 and hsp70 in addition to the number of glucocorticoid-binding sites and their affinity using glucocorticoid-sensitive and -resistant human leukemic cell lines. We showed that two of nine resistant cell lines with normal glucocorticoid-binding proteins express aberrant hsp90 and extremely low hsp70, while another seven resistant cell lines had decreased binding sites with normal hsps. These results suggest that there are at least two independent mechanisms of glucocorticoid resistance in human leukemic cell lines: the decreased ligand-binding sites and the abnormal hsps expression.

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Study of heat shock protein HSP90 alpha, HSP70, HSP27 mRNA expression in human acute leukemia cells.

Xiao K, Liu W, Qu S, Sun H, Tang J.

Department of Hematology, Tongji Hospital, Tongji Medical University, Wuhan.

The expression of three heat shock proteins (HSPs)-HSP90 alpha, HSP70, HSP27 in cells obtained from 22 patients with leukemia, K562 erythroleukemia cell line, and normal blood cells was observed by means of RNA dot blot analysis. The results showed that the expression of the HSP27 gene was enhanced in 4 cases of acute lymphoid leukemia (ALL), 7 cases of acute nonlymphoid leukemia (ANLL) and 2 cases of myelodysplastic syndrome (MDS) as compared with that of the normal blood cells, yet there was no significant difference in the HSP27 expression between the ALL and ANLL cells. The expression of HSP70 in all the 5 ALL and ANLL patients was much lower than that of the normal subjects, except 1 case of ALL and 1 case of MDS, in which the expression was obviously enhanced. All the cases including 11 ANLL, 5 ALL and 1 MDS had higher HSP90 alpha expression than the normal subjects. The enhanced expression of HSP90 alpha in leukemia cells may be associated with the active and indefinite proliferation of leukemia cells. Our results also suggest that the high expression of the HSP27 gene may not be confined to a specific type of acute leukemia.

PMID: 9389084 [PubMed - indexed for MEDLINE]

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Heat shock proteins are differentially expressed in human gastrointestinal cancers.

Ehrenfried JA, Herron BE, Townsend CM Jr, Evers BM.

Department of Surgery, University of Texas Medical Branch, Galveston 77555-0533, USA.

The heat shock proteins (Hsp) are stress-responsive genes present in all species; increases of Hsp can confer chemotherapeutic resistance to certain cancers. The purpose of this study was to determine Hsp expression in human gastric, pancreatic and colon cancers. Gastric (n = 3), pancreatic (n = 6) and colon (n = 8) cancers were extracted for RNA and protein, and Northern and Western blots performed. We found that hsp70 and hsp27 mRNA levels were differentially expressed in the gastrointestinal cancers; mRNA expression closely correlated with protein levels suggesting regulation at the level of transcription. In addition, Hsp90 and BiP proteins were constitutively expressed in the gastrointestinal cancers. We conclude that the Hsp are differentially expressed in human gastric, pancreatic and colon cancers; these increases in Hsp occur constitutively and are not the result of physiological or environmental stresses. Increases of Hsp expression in cancer cells may enhance resistance and account for the altered sensitivity of certain gastrointestinal cancers to chemotherapeutic agents.

PMID: 8528482 [PubMed - indexed for MEDLINE]

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Stress-response (heat-shock) protein 90 expression in tumors f the central nervous system: an immunohistochemical study.

Kato S, Morita T, Takenaka T, Kato M, Hirano A, Herz F, Ohama E.

Division of Neuropathology, Faculty of Medicine, Tottori University, Yonago, Japan.

This retrospective study deals with the expression of stress-response (heat-shock) protein 90 (srp 90) in a series of 148 human brain tumors. Immunohistochemical procedures were employed; cells of the human breast cancer line MCF7 exposed to hyperosmolar stress served as positive controls. Deposits of reaction products were found in the cytoplasm and they displayed a granular pattern. srp 90 was detected in 14/31 meningiomas and 5/10 breast cancer metastases to the brain. The protein was also present in 6/13 glioblastomas and 7/18 astrocytomas. In addition, a positive reaction was found in 2/10 medulloblastomas, 2/14 primitive neuroectodermal tumors, 1/11 pituitary tumor, 2/21 schwannomas and 2/11 lung tumor metastases; however, oligodendrogliomas and primary malignant lymphomas were not stained. The srp 90 was detected in Western blots of meningioma tissue homogenates. No significant immunohistochemical reaction was seen with sections of normal human cerebra, brain stem, cerebella, pituitary glands and spinal cords. These results document the expression of srp 90 by a variety of primary and metastatic intracranial tumors.

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☐ 1: J Oral Pathol Med 1998 Jan;27(1):18-22

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Expression of heat shock proteins in squamous cell carcinoma of the tongue: an immunohistochemical study.

Ito T, Kawabe R, Kurasono Y, Hara M, Kitamura H, Fujita K, Kanisawa M.

Department of Pathology, Yokohama City University School of Medicine, Yokohama, Japan.

Twenty-four specimens of squamous cell carcinoma of the tongue were immunostained for heat shock proteins (HSPs) to reveal differences in stainability among normal epithelium, dysplasia and carcinoma and to clarify the prognostic significance of HSPs in comparison with survival period, clinical stage, lymph node metastasis, histological grade, and p53 immunostaining. Normal epithelium was positively stained in the suprabasal layer for HSP60 and HSP70, but was negative for HSP27 and HSP90. Dysplastic lesions were positive for HSP27, HSP70 and HSP90, but stained variously for HSP60. In squamous cell carcinoma, the cytoplasm of suprabasal tumor cells was often positive for HSP27 and HSP90 (18/24, 17/24, respectively). Although HSP immunohistochemistry has revealed changes in HSP expression during tumorigenesis of squamous epithelium of the tongue, there was no correlation between HSP staining and survival period, stage, lymph node metastasis, histological grade or p53 immunostaining.

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Detection and distribution of heat shock proteins 27 and 90 in human benign and malignant prostatic tissue.

Thomas SA, Brown IL, Hollins GW, Hocken A, Kirk D, King RJ, Leake RE.

West Glasgow Hospitals University NHS Trust, UK.

OBJECTIVE: To determine whether it is possible to predict the behaviour of prostate tumours by identifying cellular characteristics, specifically specific heat shock proteins (HSPs). MATERIALS AND METHODS: An immunohistochemical study staining for HSP 27 and 90 was undertaken on 15 benign and 13 malignant samples of freshly frozen prostatic tissue obtained from patients with a similar age range in each group (benign, mean age 71.6 years, range 61-86; malignant, mean age 72.7 years, range 58-87). Gleason scores for the tumours ranged from 2 to 8. RESULTS: Consistent patterns of cytoplasmic staining were seen in all sections of tissue from benign prostatic hyperplasia (BPH). The stroma stained strongly positive for HSP 27, but negatively for HSP 90 and glandular epithelium showed positive apical staining for both HSPs. Stromal patterns in prostatic carcinoma tissue were similar to that of BPH tissue for both HSP 27 and 90. Areas of prostatic intra-epithelial neoplasia stained as strongly as did adjacent areas of BPH. For HSP 27, there was varied staining of individual epithelial cells, suggesting cellular heterogeneity, with an apparent reduction in staining with increasing Gleason score and invasiveness. For HSP 90, this pattern was less marked, with a predominance for positive staining throughout all grades of carcinoma. CONCLUSIONS: The distribution of HSPs, primarily HSP 27, may aid in identifying different cell populations within prostatic carcinomas and thus help forecast biological behaviour.

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